REMARKS

In the claims

Claims 16–74 are pending of which claims 52–74 are currently under examination and claims 16–51 previously withdrawn due to restriction/election. Claims 1–16 were previously cancelled without prejudice or disclaimer.

Specification

The Examiner's careful reading of the specification is appreciated. It is courteously submitted that positive actions are not necessary at this moment as the informalities in the specification do not change the scope of the claimed subject matter. However, the specification will be duly amended once allowable subject matter has been identified.

Rejection under 35 U.S.C. §112, first paragraph

The Office Action alleges that the specification does not provide a written description of the claimed subject matter and fails to comply with the enablement requirement. As such, claims 52–74 stand rejected under 35 U.S.C. §112, first paragraph. Applicants courteously traverse this rejection.

The claims of the instant application are drawn to the structural features of polypeptide libraries that are utilized in the identification of individual proteins which bind to a target of interest (as recited in claims 52–63) and a general methodology of achieving such a utility (as recited in claims 64-74). As recited in Applicants' claim 52, the system relies on individual identifier sequence amino acid tracts which are unique to said individual protein when bound to the specific target of interest. As described in the specification and in Applicants' numerous communications with the Patent Office, these identifier sequence amino acid tracts, which can be situated internally or terminally to the candidate polypeptide of interest, are used to mark and identify the presence of such candidate polypeptides. The specification teaches that the unique identifier tracts are released via

protease treatment, facilitating the identification of the protein to which it is attached. These amino acid sequences are arbitrary, and there is no required structure recited in the claims as long as they are "unique."

The Office's reliance on the *Eli Lilly* case is misplaced for reasons explained in the prior communications. For example, in *Lilly*, the claims were directed to mammalian insulin (i.e., a polypeptide) which possessed insulin activity– an aspect which was well-established in the field. The central issue in the case was whether the specification provided enough of a description to pick out those sequences with the insulin activity and distinguish them from other sequences. Without a specific generic structure, the court held the claims lacked written description.

The claimed invention revolves around a different issue. As described in the instant application, a claimed structural feature of the library is the presence of identifier sequence amino acid tract. As taught by the Applicants' instant specification, such can be arbitrary, and can possess substantially any amino acid sequence – including random or semi-random sequences, the only requisite feature be that they are "unique" sequences. See, for example, page 2, lines 36 to page 3, line 5 of the specification. In contrast to the insulin molecule of the *Lilly* case, it is not necessary for the tract have a biological activity. It is the sequence itself which has the function as a marker. Thus, any sequence of, for example, eight amino acids, when uniquely adjacent to a protein of interest, can be used to mark that protein.

Applicants' specification not only describes the structural features of such sequence identifier tracts, but also provides a method for using them as "barcodes." The barcodes are encoded for by oligonucleotides that are attached, in open reading frame, to the nucleotide sequence encoding the polypeptide of interest. Other structural elements, for example, protease sensitive-sites, which facilitate release of the peptide identifier tract, are also described. The rationale used in the design and application of such sequence tracts is also fully described by the Applicants' specification. For example, at page 4, lines 23-44, an eight-amino acid barcode sequence using 17 of the 20 natural amino acids is disclosed. A specific example is provided of a family of peptide barcodes and their corresponding oligonucleotide sequences. Example 2 contains a specific working example of barcode sequence. Another example is disclosed at page 35, lines 30–35 of the specification.

Thus, it is courteously submitted that Applicants' specification discloses the structural and functional elements of the claimed libraries.

"Combinations of sequences to form unique tracts for each [member of] the library"

Page 8 of the Office Action alleges that while the specification provides guidance for formulating unique sequence tracts for 13,824 members, it "does not describe the specific combinations...to form unique tracts for each of a billion proteins in the library." The Office Action then alleges that Applicants' specification contains "unpredictable effects in the use of single tracts." However, it is courteously submitted that the structural features described in the design of sequence tracts, such as the exclusion of stop codons and/or greater than two alternative codons, are merely exemplary and should not be taken as a limitation of the claimed invention. For example, the art recognizes the dilemma of creating "fully randomized DNA libraries" i.e., one with the possibility of having a stop codon inserted in the middle of a potential identifier sequence, since, such would merely increase the number of samples in a library without increasing the number of viable samples. Proper measures are routinely introduced into chemical/genetic libraries during both the design phase as well as the screening phase to reduce such redundancies or false positives. As such, it is courteously submitted that the structural limitations described in the Applicants' specification are not "*unpredictable effects*" but rather an approach to the rational design of the claimed libraries.

"Protease sensitive sites"

At page 11, the Office Action further alleges that "it is not apparent from the claimed unstructured protein, the sites that are sensitive to an enzyme [i.e., protease]" and relies on Eaton's incomplete disclosure to support this contention.

As previously outlined in Applicants' response to the prior Office Action, protease sensitive sites, such as ones claimed in the instant application, are well known in the art, and readily could be utilized by one of ordinary skill in the art. Such sites are used conventionally in molecular biology, e.g., to cleave tag sequences (that are used in protein purification) from proteins of interest. For example, there are numerous protease enzymes and their protease sensitive cleavage sites in commercial use, which were furbished for the

Office's examination in the form of Exhbits 1–4. See, the response to the Office Action of November 21, 2005.

Applicants respectfully submit that the aforementioned exhibits establish the commercial use and general acceptance of protease sensitive sites to provide a precise cleavage position to cleave off a leader amino acid sequence from a recombinant protein of interest. Indeed, the cited prior art references, for example, Knappik, Ring, and Markland, which are used by the Office to assess the relevant state of the art, also make use of protease cleavage agents and substrates. Applicants' respectfully submit that the utilization of such prior to the filing date of the instant application scientifically corroborates the novel methodology described herein. The Office's attempt to instill ambiguity and unpredictability into this concept is clearly at odds with the state of the art, including the Office's own interpretation of the relevant technology. Furthermore, the Office's reliance on the Eaton reference for allegedly lacking written guidance on the structural features of protease cleavage sites is irrelevant in view of the fact that this enzyme (and its corresponding cleavage site), as shown in Exhibits 2-4, is utilized commercially in protein purification. Thus, the alleged unpredictability and discrepancies are insubstantial, given the fact that Factor Xa sensitive sites are commonly used in protein purification.

The *Capon* case

As outlined in Applicants' prior response to the Office Action, it is courteously submitted that the facts at issue in this pending application parallel those of *Capon* where it is not the specific individual elements which are being claimed as necessarily novel, but it is the claimed chimeric structure and how these individual elements are arranged which provides novelty and unobviousness. Protease sequences, binding proteins, and arbitrary sequences are known, the technology of recombining sequences is mature, and the predictability factor is high. There is no basis to sustain this rejection. In essence, the present examiner's entire premise is inconsistent with federal law. Given this maturity in the field, a skilled worker could routinely screen for any variant of the claimed compounds in order to practice the instant invention in its broadest possible scope. Nothing more than routine experimentation would be required. It is therefore courteously submitted that Applicants' claims in the current form, with adequate support from the specification, fully

comply with the statutory requirements under 35 U.S.C. § 112, first paragraph, as specified in the PTO's own guidelines. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

The specification coupled with a skilled worker's knowledge provides adequate guidance to make and use the claimed libraries. The specification provides both general and specific guidance regarding the structural features and utility of the amino acid sequence identifier tracts. In the absence of evidence which demonstrates otherwise, all claims must be taken to satisfy the requirements of 35 U.S.C. § 112, first paragraph. Moreover, only one use needs to be enabled for compound claims. Here, we focus on the single chain antibody library containing unique peptide barcodes. See, Example 2 at page 29, lines 15-20 of the instant specification.

The specification provides guidance on the synthetic design and use such libraries. See, for example, Example 1 at page 26 of the specification. In view of this detailed disclosure, and the general knowledge of polypeptide libraries (for example, see the introduction at page 1 of the specification), one of ordinary skill in the art could routinely employ common combinatorial techniques to design and isolate a polypeptide of interest, for example, an antibody-binding protein as disclosed herein. See, for example, Examples 4 and 5 starting at page 36 of the specification, which disclose a methodology for screening a randomized library. In light of the disclosure on various embodiments of Applicants' claimed invention, the courts have placed the burden on the PTO to show otherwise. It is courteously submitted that the Examiner has not presented any evidence to refute the findings or the conclusions made in these supporting publications. In addition, no evidence has been presented to support the contention that the claimed compounds could not be made and used, in a manner that is commensurate with Applicants' claimed invention. Only unsupported allegations and conclusions regarding the "complexity" and "unpredictability" of the "broad genus of compounds" are provided to support the contention. There are especially weak in the face of the showing that the field of screening techniques based on protein-protein interactions is a mature one. See, page 1, line 16 to page 2, line 17 of the instant application and the operative embodiments of the claimed invention which are

disclosed in the Examples.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine with in the art. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §102

The anticipation rejection in view of Chen and Georgiou are withdrawn, however, the Office has maintained the rejection over Matthews et al. Applicants respectfully traverse the rejection.

Mathews and Wells (*Science*, **vol. 260**, pages: 1113–1117, **1993**) describe a method for identifying protease substrates using a "phage display" of proteins which contain putative protease cleavage sites. The protein construct utilized by Mathews and Wells contain the following structural elements: human growth hormone (hGH) domain–protease substrate–M13 phage protein, wherein the protease substrate comprises a protease sensitive sequence. See, Mathews and Wells, Fig. 1. The phage particles are immobilized through affinity binding of a phage surface hGH domain to an immobilized hGH binding protein. The complex is then contacted with a protease to specifically cleave the polypeptide and release the phage into the medium. Cleaved phage are then directly sequenced to determine the amino acid sequence of the cleavage site.

As outlined at page 18 of the open Office Action, the alleged anticipation rejection rests on the assumption that the linker (amino acid) sequence (GPGG[X]$_5$GGPG or GPAA[X]$_5$AAPG) of Matthews is equivalent to the *identifier sequence* claimed herein. It is courteously submitted that such assumption is grossly misplaced. It is clear that Matthews merely uses these linker sequences to fuse an "affinity protein" (such as hGH) to a target protein (such as gene III protein), peptidically cleave these fused polypeptides (by using a mutant bacterial serine protease), and randomly create GG-flanked or AA-flanked peptide libraries, which are enriched and pooled using biochemical purification. It is learnt from Table 1 of the cited reference that the "clones" of interest are identified by DNA

sequencing. See the citation of Ref. 26 in Table 1, which relates to Sanger's sequencing methodology (Sanger et al., *PNAS*, **vol. 74**, pages: 5463–5467, **1977**). The cited art reference does not utilize *identifier sequences* claimed herein to identify the polypeptides of interest. Moreover, the construct disclosed by Mathews does not recite the elements of unique identifier tracks which, "when bound to the specific target of interest [i.e., hGH binding protein]," "are flanked by one or more protease sensitive sites." Compare pending Claim 52 to the methodology used by Matthews et al.

It respectfully submitted that the libraries of Matthews and the methodology used in screening such libraries are distinct from the subject matter of Applicants' instant application. As such, the cited reference of Matthews cannot anticipate or render obvious what is claimed by the instant invention. Withdrawal of the rejection is therefore courteously requested.

Rejection under 35 U.S.C. §103(a)

The Office has maintained the rejection of claims 52–70 under 35 U.S.C. §103(a) over the cited reference of Knappik in view of Ring et al. and Markland et al. Furthermore, Applicants' method claims 71 and 72 stand rejected under the same as being unpatentable over the aforementioned references further in view of the MALDI-ToF technique of Hutchens et al.

The primary reference of Knappik's patent describes a library of modular DNA sequences that code for antibodies (and other proteins), which contain nucleotide cleavage sites. In fact, Knappik's entire disclosure is based on DNA libraries, and the utilization of such to create randomized peptide libraries. Moreover, at col. 14, lines 11–14 Knappik expressly discloses "cleavage site" as being a DNA cleavage site:

> Cleavage Site
> A short DNA sequence which is used as a specific target for a reagent which cleaves DNA in a sequence-specific manner (e.g. restriction endonucleases).

Applicants courteously submit that the cited reference does not describe protease

cleavage sites, or impart any teaching on protease sensitive sites. What Knappik discloses are separate sub-sequences in the DNA, which correspond to different protein coding domains. See, for example, col. 8, lines 20–41 of the cited reference. The DNA cleavage sites are utilized to selectively modify domains within the coding DNA sequence. See, for example, col. 10, line 656–col. 11, line 7 of Knappik. Neither Knappik et al. nor the open Office Action impart any teaching or suggestion regarding how DNA cleavage sites may serve to fulfill the role of identifier sequence amino acid tracts claimed herein. Even if such were the case, Applicants' respectfully submit that Knappik's disclosure on DNA cleavage sites is structurally distinct from the amino acid tracts claimed herein.

To establish prima facie case of obviousness, three basic criteria must be fulfilled. First, there must be some suggestion or motivation...to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.

Since the primary reference of Knappik is deficient in reciting all the claim limitations, the Office Action relies on the combined disclosure of Ring et al. and Markland to allege that claimed structural features are encompassed by the cited references. However, it is respectfully submitted that none of the cited references describe one or more individual identifier sequence amino acid tracts which are unique to said individual protein when bound to the specific target of interest. Compare Claim 52 to the teachings of Knappik, Ring and Markland. Moreover, the Office Action fails to provide a prior art publication which discloses this structural aspect along with the other limitations described in Applicants claimed libraries and methods. As such, it is submitted that the Office Action has clearly failed to establish a prima facie case of obviousness.

Applicants' further submit that the Office Action has not established that one of ordinary skill in the art would be motivated to combine the cited teachings. Even if one were to do so, a combination of such would never lead a skilled artisan to reformulate the cited references to arrive at the instantly claimed subject matter. Withdrawal of the pending rejection is respectfully requested.

Claims drawn to mass-spectrometric method

The Office Action at page 23 alleges that the claims 71 and 72, which are drawn to a mass-spectrometric method, are rendered obvious when the aforementioned references are taken together with the teachings of Hutchens et al.

The various deficiencies of Knappik, Ring, and Markland have been previously outlined. The Examiner is courteously requested to take note of these deficiencies. The additionally cited reference of Hutchens et al. is generically drawn to MALDI-ToF. See, page 25 of the open Office Action. However, since Hutchens does not describe any other structural or functional limitations of the Applicants' claimed libraries. For example, Hutchens does not disclose unique amino acid sequence identifier tracts, as claimed herein. Therefore, it courteously submitted that the primary references, even in combination with Hutchens would fail to render obvious what is claimed by the instant invention. Withdrawal of the rejection is courteously requested.

In view of the above-mentioned arguments and amendments, it is respectfully submitted that the claims in the application are in condition for allowance. However, if the Examiner has any questions or comments, he is cordially invited to telephone the undersigned at the number below.

Enclosed is a check in the amount of $1020.00 for the three-month extension-of-time fees. No other fees are believed to be due with this response; however, the Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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